The Applicant understands from the telephone interview that the Examiner agrees that claimed methods have a substantial, specific, and credible utility (i.e., that the rejection is not a utility-type rejection under both 35 U.S.C. §§ 101 and 112). The Applicant also understands from the telephone interview that the Examiner does not question that the specification adequately discloses how to perform the physical acts (i.e., administration, local or otherwise) recited in the claims.

Instead, as discussed during the telephone interview, the Examiner's rejection is based on the Examiner's belief that the specification does not include sufficient teaching to inform a skilled artisan how the methods should be performed in humans. The Applicant believes the rejection was not properly made and, even if it had been properly made, is overcome by the evidence of record following entry of this Response. These issues are separately described in the following two sections.

The Enablement Rejection was not Properly Made

The Applicant believes the rejection was not properly made because

> "*In order to make a[n enablement] rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.*" MPEP § 2164.04.

The Applicant respectfully suggests that the Examiner has done substantially nothing more than merely question whether the claimed methods can be used in humans. The Examiner has the burden to support an enablement rejection with evidence or reasoning that demonstrates that a skilled artisan would doubt the truth or accuracy of what is taught in the specification. MPEP § 2164.04.

As support for the enablement rejection, the Examiner has cited several prior art references and suggested that those references demonstrate that usefulness of the claimed methods *in vivo* cannot be predicted from results obtained *in vitro*. The Applicants respond that usefulness of the claimed methods *in vivo* is not premised on *in vitro* results obtained by the Applicant or others. The Applicant respectfully contends that the prior art references cited by the Examiner are irrelevant to the claimed methods, and that the *in vivo* activities of the agents recited in the claimed methods were known at the time this application was filed. These two issues are separately discussed in the following two sub-sections.

The Prior Art References Cited by the Examiner are Irrelevant to the Claimed Methods

The prior art references cited by the Examiner are irrelevant to enablement. Several of the articles (Mori, Zeisig, Wuyts, Akatov, and Schrauzer) are purported to "establish the general state of the art and level of predictability of alleviating a tumor in a human patient as claimed" (Office Action dated 10 December 2001; referred to in Office Action dated 3 July 2002). Each of these references discloses information about only a single compound recited in the claims and how it was used in *in vitro* studies (other than Schrauzer, which described an *in vivo* study) that are unrelated to the present invention. The Examiner correctly indicates that none of these prior art references discloses that the individual compounds exhibit tumor-alleviating activity in humans. However, this analysis misses the point of 35 U.S.C. § 112, first paragraph, enablement inquiry.

The statute does not require that the prior art teach how to make and use the invention - it requires that the Applicant's specification teach how to make and use the invention in view of what was known in the art at the time the application is filed.

The Applicants believe that the Examiner misunderstands the nature of the invention. Each of the Mori, Zeisig, Wuyts, Akatov, and Schrauzer references discloses the effects of a single biological agent (or a pair of agents including a known anti-tumor alkaloid in Mori) on tumor cells. This is not what is claimed. The Applicant claims a method that includes local administration of at least four agents to a tumor (see independent claims 1 and 66). The tumor-alleviating effect of the claimed methods is not achieved by the action of any single agent (or any pair of agents) on tumor cells. Instead, the claimed methods involve attracting immune cells of the patient to the tumor and inducing the attracted immune cells to exhibit a type 1 inflammatory response (see items 29 to 39 of the enclosed Declaration of Dr. Eugene Roussel). It is the patient's (inflammatory) immune response - not the agents recited in the claims - that directly alleviate the tumor. Because none of the Mori, Zeisig, Wuyts, Akatov, and Schrauzer references disclose a method of inducing an anti-tumor type 1 inflammatory response, they are irrelevant to the claimed methods.

The Dermer reference cited by the Examiner is irrelevant, in that it discusses purported incongruities between tumor cell lines and tumors *in vivo*. Enablement of the

claimed methods is not dependent on information derived from tumor cell lines. The Examiner cites Dermer as a further reason why the prior art references she cites do not disclose the invention. The Applicant agrees that the combined references do not disclose the claimed methods, but believe that this point is irrelevant to the fact that the specification teaches how to make and use the claimed invention.

The Jain reference cited by the Examiner is irrelevant, in that it discusses problems inherent in systemically-administered anti-cancer therapies. The claimed methods recite local administration to a tumor in a human patient, and the concerns discussed in Jain do not apply to locally administered therapeutic agents. For the claims (e.g., claims 41-43 and 49-66) that recite additional steps comprising not-necessarily-local administration of a nutrient or a memory cell-inducing agent, local administration to the tumor is not necessary for the administered agent to have its intended (i.e., nutritional or memory-cell inducing) effect. Thus, the Jain reference is irrelevant to enablement and utility of the claimed methods.

The Examiner suggests in the Office Action dated 10 December 2001 that the cited references indicate that the agents recited in the claims may kill tumor cells *in vitro* but not in human patients. The Applicant contends that, to the contrary, each of the cited references appears to suggest (if not explicitly indicate) that the corresponding agent may be useful for treating human cancer. None of these references appears to disclose any information regarding the predictability that *in vitro* results can be replicated *in vivo*, as the Examiner suggests.

For the foregoing reasons, the Applicant believes that the prior art references cited by the Examiner are irrelevant to the issue of whether the specification adequately enables the claimed methods.

The *in Vivo* Activities of the Agents Recited in the Claims were Known

The Examiner cited the prior art references discussed in the previous sub-section for the proposition that the *in vivo* activities of the agents recited in the claimed methods could not be predicted from *in vitro* results. However, enablement of the claimed methods does not depend on extrapolation of data collected *in vitro*. The *in vivo* pharmacological and physiological activities of each of the agents recited in the claims was known for the dose ranges disclosed in the application at the time the application was filed.

As set forth in greater detail in items 30 to 38 of the enclosed Declaration of Dr. Eugene Roussel and the references cited therein, the activity of each of the agents recited in the claims was known in the art. The Applicant does not claim to have discovered any previously unknown activity of these agents. To the contrary, the claimed methods rely on the synergistic known activities of the agents to achieve a result in a way that was not previously recognized by others. The specification describes suitable dose ranges for the agents recited in the claims (e.g., see page 13, line 23, through page 15, line 19 for appropriate doses of antigen-releasing agents; see page 16, line 14, through page 17, line 2 for appropriate doses of leukocyte attractants; see page 18, line 13, through page 19, line 3 for appropriate doses of type 1 inflammatory response-promoting agents). Furthermore, two prophetic examples of alleviating tumors in humans are provided. The Applicant respectfully contend that this information is sufficient for a skilled artisan in this field to practice the invention that is claimed.

The Applicant believes that the Examiner may underestimate the abilities of skilled artisans in this field. The field of the invention is alleviation of tumors in human patients. Skilled artisans in this field are not simply biochemists or even ordinary medical doctors. As set forth at items 8 to 10 of the enclosed Declaration of Dr. Eugene Roussel, skilled artisans in this field are clinical oncologists who have a great deal of training and experience. The Applicant respectfully contends that skilled artisans in this field are able to use the information that is available in the art to select appropriate doses of the claimed agents in order to achieve the effects that are described in the specification.

In summary, because the *in vivo* activities of each of the agents recited in the claims was known in humans before the Applicant made his invention for the dose ranges disclosed in the specification, the skilled artisan is able to select agents and doses thereof such that each of the agents would exhibit its known activity in a human. In view of the teachings provided in the specification regarding the interactions of the activities attributable to the agents, the skilled artisan would understand that the methods discovered by the Applicant would operate in the way described in the specification. Thus, the specification teaches the skilled artisan how to perform the claimed methods in a human.

The Enablement Rejection is Overcome by Evidence of Record

The Applicant respectfully contends that the totality of the evidence of record demonstrates that the specification adequately teaches a skilled artisan how to practice the claimed methods in a human patient. The reasoning supporting this contention is set forth in the remainder of this section.

Even if the Examiner's contention were correct that the specification, standing alone, does not adequately disclose how to perform the claimed methods in a human patient, the specification is not properly viewed standing alone. Instead, the specification must be read in view of what was known in the art at the time the application was filed. As discussed above and in the enclosed Declaration of Eugene Roussel (e.g., see items 29 to 47), the specification teaches what was not already known in the art about how to perform the claimed methods in a human. Thus, considered in view of what was already known at the time the present application was filed, the specification discloses all that was needed to practice the claimed methods.

The Examiner suggests that the specification "does not give any evidence of administration leading to the alleviation of a tumor **in a human patient**". In addition to the prior art arguments disposed of above, the Examiner's contention appears to be based on the lack of a working example in the specification and the Examiner's belief that practicing the invention would require undue experimentation. The Applicant addresses these two issues in the following two sub-sections.

Lack of a Working Example

Regarding lack of a working example,

> "*[L]ack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement.*" MPEP § 2164.02.

> "*The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.*" *Gould v. Quigg*, 3 USPQ2d 1302 at 1304 (Fed. Cir. 1987.

The Examiner is correct that no working examples are included in the specification. However, the Applicant respectfully contends that there is sufficient guidance (i.e., other than working examples) in the specification and the prior art to teach a skilled artisan how to use the methods described therein to alleviate a tumor in a human. One need only perform the local administration steps disclosed in the specification (and recited in the claims), in the order disclosed and claimed, to induce an anti-tumor type 1 inflammatory response in a human patient.

In addition, operability of the claimed methods can be predicted by analogy to another tumor alleviation method that induces an anti-tumor type 1 inflammatory response in a human patient. As further described in item 24 of the enclosed Declaration of Dr. Eugene Roussel, numerous groups of investigators have administered Bacillus Calmette-Guerin (BCG) to human patients afflicted with superficial bladder tumors. In a large number of these patients, the tumors were eradicated. Studies by others demonstrate that BCG exerts its anti-tumor effect by inducing a localized type 1 inflammatory response in the vicinity of the bladder tumor. There is no evidence that BCG cells exert any anti-tumor response of their own (i.e., the Bacillus cells to not appear to exhibit anti-tumor cell cytotoxic activity). These results demonstrate that induction of a type 1 inflammatory response in a human tumor leads to alleviation (or even eradication) of the tumor. Thus, a skilled artisan would accept that induction of a localized type 1 inflammatory response in a tumor would lead to alleviation or eradication of the tumor.

As set forth in item 32 of the enclosed Declaration of Dr. Eugene Roussel, the skilled artisan would understand that interferon-gamma inhibits activation of Th2 cells and suppresses development of a type 2 inflammatory response, and that local administration of interferon-gamma and another type 1 inflammatory response-promoting agent (e.g., interleukin-2, which induces proliferation of Th1 cells, or tumor necrosis factor-beta, which stimulates Th1 cell activation and enhances expression of interferon-gamma receptor on T cells) to a tumor would lead to induction of a localized type 1 inflammatory response in the tumor.

In summary, even though the specification does not include a working example whereby an anti-tumor type 1 inflammatory response was induced using the methods recited in the claims, the skilled artisan in this field would understand that the performing the steps

recited in the claimed methods induces a type 1 inflammatory response in a tumor in a human patient, and that this induction will lead to alleviation or eradication of the tumor in the patient.

Undue Experimentation

In the Office Action dated 10 December 2001, the Examiner lists the *Wands* factors, but it is not clear how the Examiner balanced or otherwise relied on those factors. The Applicant states below how each of the *Wands* factors applies to the claimed invention, and then summarizes how the factors balance in this situation.

Wands Factor 1) the breadth of the claims:

The claims are directed to methods of locally administering known agents to substantially any human solid tumor. The agents are known. Local administration methods are known. Although there are a variety of human solid tumor types, the tumor type is not relevant to the breadth of the claims in this application because, regardless of the tumor type, the same underlying mechanism of action (induction of a localized anti-tumor type 1 inflammatory response) is believed to responsible for tumor alleviation. Thus, although the claimed methods are useful against a wide variety of tumor types, the underlying method is similar for all of these types, and the agents recited in the claims are effective against substantially all solid tumor types. Therefore, the breadth of the claims does not require that experimentation be performed.

Wands Factor 2) the nature of the invention:

The claimed methods relate to a therapeutic method. Therefore, some degree of individual variation among patients is inevitable. However, this situation is no different than any other therapeutic method. Medical practitioners routinely prescribe a dose of a therapeutic agent to a patient, observe the response (including any side effects), and modify the dosage or identity of the therapeutic agent depending on the individual patient's response. No greater amount of variation is expected for the claimed methods than for any other therapeutic method. The Applicant contends that normal therapeutic practice includes only routine 'experimentation.'

Wands Factor 3) the state of the prior art:

Each of the agents recited in the claims are known, and multiple embodiments of several of the agents (e.g., antigen-releasing agents and leukocyte attractants) are known, as were their corresponding pharmacological and physiological activities. Methods of locally administering the agents to tumors are known. Thus, there is no individual step of the claimed methods that could not have been performed in view of what was known in the prior art. Patentability of the claimed methods arises from the combination of the known agents and methods of administration to achieve an effect that was not previously recognized by others as being achievable using the known agents and methods. Thus, what was not supplied in the Applicant's specification was known in the prior art.

Wands Factor 4) the level of one of ordinary skill:

As set forth in items 8 to 10 of the enclosed Declaration of Dr. Eugene Roussel, the skilled worker in the field of the invention is a clinical oncologist, who will have earned a medical degree, often one or more other advanced degrees, will have performed a medical internship under the guidance of one or more other experienced clinical oncologists, and will likely have several years of additional experience. Clinical oncologists are accustomed to carefully observing cancer patients and the effects that therapy administered to those patients has upon the patients and their tumors. Such oncologists are also accustomed to modifying the anti-cancer therapeutic regimes of patients having tumors to account for individual differences in patient responses to the regimes. Thus, the level of the ordinarily skilled worker in the field of the invention is very high.

Wands Factor 5) the level of predictability in the art:

As noted above, the responses of individual patients to pharmacological agents and combinations of such agents is known to vary to some degree. However, the activity attributable to each of the agents recited in the claims was relatively well known at the time the application was filed (as set forth in items 30 to 38 of the enclosed Declaration of Dr. Eugene Roussel). Among the novel features of the claimed methods is the <u>combination</u> of agents and (in some embodiments) the order and timing of administration of the agents.

Wands Factor 6) the amount of direction provided by the inventor:

The specification discloses the types of agents, order of administration, useful dose ranges, and timing of administration that must be followed in order to achieve the asserted utility. At least one example of each type of agent (and often several examples) are disclosed. Appropriate dosage ranges are given. Two prophetic examples are given. It is not practical to disclose the exact dosages of the various agents that would be appropriate to administer to every possible patient or for every possible size or location of tumor. However, determination of these dosage values is among the functions that are normally performed by skilled workers in this field. The specification provides sufficient guidance that the skilled worker can select appropriate agents, doses, dosing schedules, and methods of administration to practice the claimed methods.

Wands Factor 7) the existence of working examples:

The Examiner correctly points out that the specification does not include working examples. However, the claimed methods have not yet received regulatory approval (or commercial funding) that would permit ethical demonstration in humans. Nonetheless, two prophetic examples are provided, and those examples demonstrate to the skilled artisan how the claimed methods can be employed. Variations on the exemplified methods are within the level of ordinary skill in the field of clinical oncology, particularly in view of the other information disclosed in the specification regarding the identities, amounts, and known activities of the agents to be administered to a patient. Furthermore, as set forth in items 48 to 50 of the enclosed Declaration of Dr. Eugene Roussel, a skilled artisan would accept studies in the prior art as proof of the principle by which the claimed methods are disclosed to operate, and would expect the claimed methods to be operable, even in the absence of working examples.

Wands Factor 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure:

As set forth in items 41 to 47 of the enclosed Declaration of Dr. Eugene Roussel, the variables in the claimed methods include i) the identities of the agents selected for an individual patient; ii) the precise doses to be used for each patient; iii) the method by which administration is achieved; iv) the order in which the agents are administered; and v) the timing of the administrations.

Any of the agents disclosed in the specification should be suitable for use in any patient (barring, e.g., allergies). For each of the agents, the skilled artisan may choose one embodiment of the agent over another for a particular patient (e.g., depending on the location of the tumor), but such selections are merely routine therapeutic choices.

The dosage of the agent to be used will depend on the identity of the agent, the size, physical nature, and degree of severity of the tumor, the state of the patient's health, and each particular patient's response to the agent. Selection of dosages of anti-cancer agents is part of the routine work of a clinical oncologist. Thus, the 'experimentation' associated with dosage selection is no more than is normally present in the field of clinical oncology.

The method or route of administering agents to patient having a tumor will depend at least on the location, size, and nature of the tumor. Selection of an appropriate method of local administration is merely a normal interventional choice among clinical oncologists.

The order in which the agents are administered is not critical, except where indicated in the specification. Also, the timing of administration of the various agents recited in the claims would be clear from the specification, as explained in item 46 of the enclosed Declaration of Dr. Eugene Roussel.

Summary of Wands Factors

All of the methods and agents needed to practice the invention were known at the time the present application was filed. The level of skill in the field of the invention is very high. The specification provides the skilled artisan in this field with significant guidance (including examples), the guidance stopping at the point at which clinical oncologists are accustomed to varying a disclosed treatment for an individual cancer patient. The skilled artisan would not be hampered by the absence of working examples, and could use the prophetic examples in the specification to guide customization of the claimed methods for an individual patient. The Applicant respectfully contends that the specification discloses so much of how the claimed methods should be performed that there is nothing left for the clinical oncologist to do but to make routine agent-selection, dosing, and administration decisions customized for the patient being treated. Because this level of customization is routine in

clinical oncology, the Applicant contends that any experimentation that is necessary to practice the claimed invention is not undue.

Summary

The Applicant requests that the Examiner consider all of the evidence of record (including the specification, the Applicant's response to the Office Action dated 10 December 2001, the present Response, the enclosed Declaration of Dr. Eugene Roussel, the content of the prior art, and the level of skill in the art) and reconsider her contention that the skilled artisan would be unable to make and use the claimed methods for their intended purpose in view of what is disclosed in the specification. The Applicant respectfully contends that the Examiner's contention cannot be supported in view of the evidence of record.

The Applicant respectfully submits that the rejection of the pending claims has been overcome or is now inapplicable, and that each of claims 1-66 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

EUGENE ROUSSEL

20 September 2002 By: _____

(Date)

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